the State of California. Obviously, such an indefinite grant of power is void by reason of its indefiniteness, even if it might otherwise be valid.

CALIFORNIA CHIROPRACTIC ACT UNCONSTITUTIONAL

From what has been said it would seem as if the initiative Chiropractic Practice Act of California of 1922 is unconstitutional. While it is true that the Act contains the usual saving clause, providing that if any part of the Act is declared unconstitutional, the remainder of the Act will not be affected thereby, it would seem impossible in the present instance to find any part of the Act constitutional if the very groundwork on which the whole structure rests is cut away from it, and that is the effect of finding that the Act fails to provide a proper foundation through a sufficient definition of the subject-matter of the Act, chiropractic.

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ACUTE NICOTIN POISONING

AS NOTED IN THE MANUFACTURE AND USE OF NICOTIN INSECTICIDES

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DISCUSSION *by C. D. Leake, Ph. D., San Francisco; C. H. Thienes, M. D., Los Angeles; P. J. Hanzlik, M. D., San Francisco.*

AS nicotin has gained popularity as an insecticide in the viticultural districts of the interior valleys of California during the season 1931-1932, there have been some newspaper reports of poisoning of persons using nicotin insecticides. Having had no contact with these outside cases, I can say nothing about their symptoms; but as chemist in the research laboratory of a Fresno concern manufacturing large quantities of nicotin insecticidal dusts, I may give my own experiences with acute nicotin poisoning and my observations of poisoning of men engaged in handling nicotin in the preparation of such dusts. Before considering these few cases, I shall review the chemistry and pharmacology of the constituents of those insecticides which contribute to the symptoms of acute poisoning.

NICOTIN POISONING BY INHALATION

Nicotin occurs in tobacco leaves and stems, as the malate and citrate. In most commercial preparations it occurs as the basic alkaloid or as the sulphate, and in cases of accidental poisoning it probably enters the body in one of these two forms. By far the greater number of recorded cases of nicotin poisoning have resulted from accidentally swallowing the alkaloid or its sulphate; the literature is greatly lacking in reports of poisoning by inhalation or skin absorption. Though the effects of inhalation of tobacco smoke are popularly attributed to the action of nicotin, a review of the literature on the toxicity of tobacco smoke shows an inclination to the theory that many of the toxic symptoms are due to the action of pyridin bases, of which some eight or ten are known to be formed on the combustion of tobacco. Wahl [1] states that the action of tobacco smoke is not pharmacologic but psychic, owing to taste, odor, and visual sensations. Poisoning by nicotin, pure and simple, then, is rare; but tobacco poisoning is very common and has probably been experienced in a mild degree by every smoker in first acquiring the habit. For this reason the cases of poisoning by inhalation of the alkaloid are hardly comparable with those resulting from the inhalation of tobacco smoke. In this connection it was observed, in the preparation of nicotin dusts, that persons habituated to the use of tobacco were not less susceptible to the action of nicotin than were nonhabituated persons. As the period during which the persons observed were in contact with nicotin vapors was not great, I cannot confirm the observations of Wahl [1] that nicotin has a cumulative effect.

NICOTIN POISONING BY SKIN ABSORPTION

In the use of nicotin preparations in various forms, there have been noted occasional cases of poisoning by absorption through the skin. Blyth and Blyth [2] note nicotin poisoning from the common practice of the peasantry in many parts of England of applying tobacco to stop the bleeding of wounds and also as a poultice to local swellings. This practice is certainly not limited to English peasantry, for the application of tobacco to insect bites, snake bites, and dog bites was by no means unknown to American pioneers and is still carried on to some extent by persons who do not avail themselves of the services of a physician. Occasional cases of poisoning of persons handling nicotin have been noted from absorption of the alkaloid through the skin, followed by characteristic symptoms, when the person handling the nicotin failed to wash the material off his hands immediately. In this local plant, where nicotin dusts are manufactured, particular precaution is taken that none of the liquid comes into contact with the body. Heavy rubber gloves are worn by persons handling nicotin, though this is not an absolute assurance against contact with the liquid, for nicotin attacks rubber to the extent that thin rubber gloves are of no use, whereas heavy rubber gloves are of no use after twenty-four hours in contact with 95 per cent nicotin. The manner in which the person using nicotin-dust insecticides handles the material may be contributory to inducing toxic symptoms. I have noted that in transferring the dust from the container to power dusters it is frequently taken up by the double-handful, the person getting his hands in contact with the nicotin as well as getting his face close to the mouth of the container, from which there is often an evolution of nicotin vapor after release from confinement in a metal container.

SYMPTOMS

The symptoms resulting from nicotin poisoning are considered to be due to the direct influence of the alkaloid on the nervous system. The re-

corded symptoms of nicotin poisoning are that there is first headache, then giddiness, numbness, disturbance of vision, torpor, and quickened respiration. After about half an hour there is a feeling of faintness, intense depression, weakness, cold extremities, and nausea. In cases of my own observation the first symptoms complained of were giddiness, quickened respiration, and nausea. After a variable period the patient usually manifested intense depression with continued nausea and vomiting, though vomiting did not always occur until induced by chemical or mechanical means. Difficulty of respiration was not relieved by artificial respiration, but increased regularly. Although convulsions are said to accompany these other symptoms, I have not seen any convulsions in these acute cases, perhaps due to the small amount of nicotin absorbed. During my laboratory experience in working with nicotin, I noted that excessive secretion of saliva and tears and an aqueous nasal discharge preceded any nausea or other recorded symptoms. The symptoms enumerated by Witherstine [3] are: first, nausea and vomiting; quick, deep, then labored respiration; great muscular relaxation, giddiness, mental confusion, restlessness, feeble circulation, general depression and, occasionally, clonic convulsions (of spinal origin) followed by complete loss of reflexes, these varying, of course, with the amount of nicotin and manner of absorbing it.

DOSAGE

The quantity of nicotin necessary to produce characteristic symptoms is an undetermined factor. It is known that some individuals do not react normally to nicotin, but it has been observed that persons in whom the digestive system is not in good order are more susceptible than others. It has also been found that some men, otherwise apparently normal, cannot be exposed to the least nicotin fumes without becoming sick. It has been stated by Dworzak and Heinrich [4] from autoexperiments that one milligram of the alkaloid produced unpleasant sensations in the mouth and throat, and salivation; two milligrams produced headache, giddiness, numbness, dullness of hearing, and quickened respiration; with three to four milligrams there was a feeling of faintness, intense depression, and purging. One experimenter had shivering of the extremities, muscular weakness, cramps of muscles of the back, and creeping sensations about the arms. Wahl [1] stated that the smallest dose that will begin to produce noticeable effects is one to two milligrams of the pure base. He stated that doses of three to four milligrams taken for several days produced greater effects with each successive dose; it was on this observation that he based his theory that nicotin is cumulative in the body.

Nicotin is absorbed into the blood and excreted unchanged. In experiments with guinea pigs, Noether [5] found that nicotin injected subcutaneously was found in greatest concentration in the urine, with a considerable amount in the intestine, and detectable amounts in the liver and lungs. After parenteral injection in man, nicotin appeared in the urine within one and one-half hours and was eliminated continuously by the kidneys for about ten hours. After inhalation, considerable amounts of nicotin quickly appeared in the urine, the time of elimination being about the same, regardless of the smoking habits of the individual. Noether further maintained that there was no evidence of an accumulation of nicotin in the body and that during the night the body again becomes nicotin free. A report of five cases of poisoning resulting from drinking nicotin insecticide was made by McNally.[6] At necropsy of one case the stomach was found to contain 0.77 gram nicotin, in another, 4.96 grams. As nicotin is unaltered by putrefaction, its presence may be detected a long time after death; Orfila [7] detected it in an animal two or three months after death.

PHYSIOLOGIC ACTION

The physiologic action of nicotin is a brief primary stimulation of the spinal cord, medullary centers and, in particular, the ganglia of the sympathetic and vasosacral autonomic system, followed by depression of the same nerve cells. These account for rise in blood pressure through vasoconstriction, glandular stimulation, and excitation of involuntary muscle tissues, including those of the alimentary tract and bladder, which small amounts of this alkaloid customarily produce.[8]

A 1:5000 solution of nicotin base was found by Savadskii [8] to produce a considerable vasoconstriction of the coronary vessels. Hett [9] observed that nicotin acts (*a*) through an effect on the vagus, spontaneously reversible and prevented by atropin, (*b*) through a disturbance of the nervous mechanism of the heart, and (*c*) through direct damage to the heart muscle tissue. Nicotin produces a muscular rigidity which can be completely and quickly resolved by the action of cocain.[10] In skeletal muscle, nicotin was observed [11] to produce fibrillary twitchings on single shocks by induction. As these phenomena do not occur in totally curarized muscles, it was concluded that they must be due to a stimulating action of nicotin on the motor nerve-termination apparatus. They were dependent on the amount of nicotin and the period of its action, becoming less marked as poisoning progressed, and often did not appear when very high concentrations were used. In very dilute solutions, nicotin exerts a stimulating action on the peripheral motor apparatus. In the early stages of poisoning, the stimulation wave is lessened. With increasing concentration of the nicotin the stimulation wave and the fatigue become greater. All these actions are not noted after curarization. It is thus concluded that nicotin acts on the true muscle substance, first as a stimulant but finally produces paralysis. The amount of nicotin required to produce action of the muscle alone is much greater than that required to produce action by the nerve-ending.

TREATMENT

The treatment of nicotin poisoning varies considerably under different conditions. An antidote for nicotin poisoning, as printed on the labels of a popular brand of nicotin sulphate, is as follows: "Drink warm water freely, then empty stomach by causing vomiting or by stomach tube. Give strong coffee or tea. In severe cases, use warm applications to chest and extremities and cold applications to head, give 1/30 grain strychnin tablet in water every hour until relieved, or until four tablets have been taken." Witherstine [3] recommends that if there is no free emesis, apomorphin hydrochlorid be given hypodermically and the stomach washed out with tannic acid solution or strong tea or a solution of iodin in potassium iodid. To hasten elimination he recommends giving spirits nitrous ether, 60 minims, or give water freely. To counteract the symptoms he suggests a hypodermic injection of strychnin nitrate, 1/25 grain, or tincture nux vomica, 30 minims, by mouth, and keep patient in recumbent position with warm applications to chest and extremities and cold applications to head. As these methods apply very well to cases in which the poisoning has resulted from swallowing the nicotin, it appears that several are superfluous for treatment of poisoning following absorption by the skin or the mucous membrane of the respiratory tract. In the former cases, washing the stomach and inducing emesis by means of apomorphin hydrochlorid seem to have as their object the removal of nicotin from the stomach; administering tea and coffee and tannic acid solution result in chemical precipitation of the alkaloid as the insoluble tannate; and the iodin-potassium iodid solution also forms an insoluble compound with nicotin. In cases of poisoning by inhalation and skin absorption these would not be of use. The object should be to hasten elimination and neutralize the symptoms.

In treatment of the ten persons suffering from acute nicotin poisoning who were brought to the plant laboratory for emergency treatment, the patient was first relieved by inducing vomiting by having him take large quantities of warm water into the stomach. On only one occasion was it necessary to use a hypodermic injection of apomorphin hydrochlorid, 1/10 grain, to induce emesis, this chiefly to relieve the patient rather than an attempt to remove any poison from the stomach. The next step was to give strychnin nitrate, 1/30 grain, hypodermically, if the patient was not relieved within fifteen minutes. On one occasion atropin hydrochlorid, 1/150 grain, was given hypodermically instead of strychnin nitrate. It appeared to have no advantage over strychnin as an antidote. All medication was given with the advice of a physician. One patient, an elderly man of weak physique, would not consider treatment, and when approached with syringe and needle for hypodermic injection of strychnin nitrate he fought vigorously and screamed at the idea of giving him anything hypodermically. He explained afterward that his dread of the sight of a hypodermic needle was because of the apparent pain which his wife suffered on the frequent occasions of hypodermic medication for treatment of mammary carcinoma. As he would not knowingly permit any medicine to be given to him, strychnin sulphate, 1/10 grain, was dissolved in half a glass of water and he was persuaded to drink it on the promise that some water in his stomach would relieve the nausea. The action of the strychnin in this case was, of course, slower than when given hypodermically, but the patient reported on the following day that all disagreeable symptoms were relieved within two hours after taking the solution of strychnin sulphate. As a final emergency aid in these acute cases, the patients were sent home with instructions to remain quiet for at least twenty-four hours, to drink large quantities of water with an occasional saline diuretic, and, without fail, to call their physician if other symptoms occurred. In none of these ten cases of acute nicotin poisoning were the patients unable to return to work on the following day, though often complaining of weakness resulting from increased purging during the preceding night. All symptoms of nicotin poisoning apparently were absent after forty-eight hours.

As the ten cases of nicotin poisoning which were observed in connection with the manufacture of nicotin insecticidal dusts presented only acute symptoms which were readily relieved by administration of physiologic antagonists, it is concluded that poisoning by inhalation or skin absorption of nicotin in the course of its use in open-air application as an insecticide is not likely to present symptoms approaching the moderate severity of the acute symptoms resulting from breathing air and handling liquids having a high concentration of nicotin base.

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DISCUSSION

C. D. LEAKE, Ph. D. (University of California Medical School, San Francisco).—With the growing application of pharmacology to fields other than medicine, such as rodent control, fruit spraying and fumigation, and food preparation, it is imperative that the medical profession keep abreast of developments along these lines in order to be prepared for the occasional untoward effect likely to happen to humans who may incur accidental poisoning from the chemicals involved. Opportunity should, therefore, be afforded by medical journals for notes by qualified experts on recent advances in work of this sort. Much of such information is not called to the attention of physicians. For example, if J. C. Munch's admirable survey of thallium toxicity (*Tech. Bull.* No. 238, United States Department of Agriculture, Washington, April, 1931) had been brought to the notice of California physicians, some of the recent difficulties with the use of this poison in rodent control might have been avoided. Similarly, many public health reports cover work on the toxicity of new commercial chemicals of possible danger to man, and these should be occasionally reviewed for physicians. Mr. Stevenson's paper on nicotin poisoning may be found to contain many points of interest to the average practitioner. It is the sort of expert survey on a practical pharmacologic problem which should appear more frequently in general medical journals.

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C. H. THIENES, M. D., Ph. D. (University of Southern California School of Medicine, Los Angeles).—Because of the rapidity with which death follows the taking of a large dose of nicotin, physicians are inclined to consider that any efforts which might be expended are of no avail, that such cases as might recover under treatment would have recovered without treatment. The cases reported in this paper would be classed in the latter category. In some cities physicians are shirking their duty in the care of cases of acute poisoning by sending them to municipal emergency hospitals. This loss of time is not infrequently responsible for the death of patients whose lives might have been saved by immediate treatment. Progress in the prophylaxis and treatment of cocain poisoning, following the work of Tatum and coworkers with barbituric acid derivatives, and the recent reports by Haggard and others of the value of apomorphin in strychnin poisoning indicate that the fatalistic attitude of many members of the profession toward acute drug poisoning is founded in part on ignorance and in part on the lack of intensive studies of such problems in experimental laboratories. In this connection it may be stated that tests of central nervous system depressants against nicotin poisoning in the rat, now being made in this laboratory, suggest that further progress may be expected in this direction.

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P. J. HANZLIK, M. D. (Stanford University School of Medicine, San Francisco).—Reports of cases of poisoning are always interesting and important, especially when they deal with personal experiences and special conditions of using a poison. Mr. Stevenson's personal experiences with nicotin confirm the well-known actions of this poison, and the use of it under his conditions has not changed the actions in essential particulars. It will not be generally admitted, however, that the systemic effects of tobacco smoke are not due essentially to nicotin. Anyone unconvinced of this should compare the effects on a frog exposed to tobacco smoke with another frog which has received nicotin. Moreover, human cases of tobacco poisoning have faithfully recapitulated all the symptoms of nicotin poisoning. While there are other potentially toxic constituents in tobacco smoke, the quantities are so small as to render their significance practically unimportant. Any psychic and euphoric effects are not peculiar to tobacco smoking, or of importance in acute poisoning.

In the treatment of nicotin or tobacco poisoning, too much reliance should not be placed on strychnin. Its use is mainly empirical, because it cannot overcome the paralytic effects of nicotin on the respiration and ganglia, which first of all have been powerfully stimulated, then depressed and paralyzed by the poison, and the paralysis is apt to be widespread and complete. The supposed circulatory stimulation of strychnin is scarcely worthy of consideration here. It is possible that, through central nervous stimulation, strychnin may be of aid in cases of partial or incomplete nicotin poisoning by promoting recovery from general weakness. However, if the poisoning is not complete, recovery occurs frequently without treatment. Paralytic cases are commonly and rapidly fatal. To promote recovery from the general weakness commonly accompanying nonfatal cases of nicotin poisoning, complete rest and drinking strong black coffee will generally suffice. In any case, the treatment of acute nicotin poisoning must be early and speedy to be effective: if the poison has been swallowed, gastric lavage with potassium permanganate (1:2000) solution (especially if vomiting has not occurred) rest, external heat, and strong hot coffee; artificial respiration, caffein and digitalis, if necessary. Caffein is a safer respiratory and central stimulant than strychnin. If the poisoning has occurred from parenteral administration, permanganate is not used, but reflex and direct stimulation of the respiration and circulation, and the use of general supportive measures, are indicated.

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MR. STEVENSON (Closing).—Though it may not be generally admitted that the systemic effects of tobacco smoke are not due essentially to nicotin, one should not ignore the fact that numerous active compounds are formed on the pyrolysis of the nitrogenous constituents of tobacco. Of these nitrogenous bases, pyridin, the basic nucleus of the nicotin molecule, occurs in largest quantity. Popp and Contzen (Estimation of Nicotin in Tobacco and Tobacco Smoke, Chem. Ztg., 46:1001-2, 1922) found that many of the alkaloidal precipitants cannot be used for the determination of nicotin in tobacco smoke. This is particularly true of silicotungstic acid because this reagent also forms an insoluble compound with pyridin, which was found in considerable quantity and accordingly gave inaccurate results. Many textbooks of materia medica assert that pyridin, pyrrole, quinolin, and isoquinolin occur in tobacco smoke. The physiologic action of pyridin is said to be similar to that of piperidin, but more energetic. It produces paralysis of the motor nerves by its effect on the motor centers. There are also destructive changes in the blood corpuscles, and paralysis of the heart.

It was asserted that any psychic or euphoric effects are of no importance in acute poisoning. I do not agree with Wahl that pure nicotin alkaloid has a psychic effect, but the majority of information at my disposal agrees that a psychic reaction is to be obtained from tobacco smoke. My object in drawing attention to the physiologic action of the products of pyrolysis of tobacco and the psychic action of tobacco smoke is to emphasize the all too common error of considering nicotin poisoning as synonymous with tobacco poisoning. This should not be considered true any more than we might consider the action of opium as being identical with that of any one of its constituent alkaloids.

It is hoped that the researches of Doctor Thienes will clear up some of the inconsistencies that occur in regard to suitable physiologic antagonists to nicotin poisoning.